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610 IMMUNE BIOMARKER ANALYSIS OF RP1 IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background RP1 is a novel, enhanced potency, oncolytic version of HSV-1 engineered to express human GM-CSF and GALV-GP R-.[1] RP1 + anti-PD1 therapy combination has resulted in deep and durable responses, including in melanoma patients who have previously failed prior anti-PD1 therapy.[2] Here we present biomarker data from the ongoing clinical trial of RP1 + nivolumab (nivo).

Methods Tumor biopsies were taken pre-treatment and at 43 days after the first dose of RP1. The tumor immune microenvironment (TIME) was analyzed IHC for CD8 (SP57 clone, Ventana) and PD-L1 (PD-L1 IHC 28-8 pharmDx by Agilent) and by gene expression analysis using the NanoString IO360 panel. The tumor inflammation signature score (TIS) was also calculated using an 18 gene signature.[3] Systemic anti-tumor immunity was assessed using PBMCs by sequencing the CDR3 regions of human TCRβ chains using the immunoSEQ assay. Correlation analysis of baseline tumor PD-L1 and CD8 status versus clinical response was also performed.

Results A consistent increase in CD8 and PD-L1 expression in the tumor was observed in most of the tested biopsies (30/44), which generally appeared to be co-located. These increases were observed both in superficial lesions and visceral tumors, including in the liver. A notable reversal of CD8 T cell exclusion was observed in a melanoma patient who failed prior ipilimumab and nivo treatment. Clinical responses were independent of baseline CD8 T cell infiltration, PD-L1 expression levels, and prior anti-PD-1 therapy. Gene expression analyses of tumor biopsies (n=11) demonstrated significant increases in the expression levels of genes associated with innate and adaptive immune activation and genes previously reported to be associated with responsiveness to anti-PD1 therapy, particularly CD8, CXCL9, CD27, and TIGIT, as well as consistent increases in TIS. TCR sequencing of PBMCs revealed expansion of pre-existing T cell clones and the appearance of new clones with 20-80% of these changes being newly detected clones. Expansion of new clones (n=170) was observed in a melanoma patient who had a complete response.

Conclusions The biomarker data indicate broad immune activation by RP1 + nivo. Clinical responses are independent of baseline PD-L1 expression and associated with increases in gene signatures associated with cytotoxic T, NK, and Th1 cells. The data indicate the potential for broad utility of RP1 in a range of tumor types, including in patients with primary or acquired resistance to immune checkpoint blockade.

Trial Registration NCT03767348

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Ethics Approval The study was approved by the institutional review board or the local ethics committee at each participating site. Informed consent was obtained from patients before participating in the trial.

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